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**14. ABSTRACT**

The goal of this project titled, ''Exploring Brain Mechanisms Underlying Gulf War Illness (GWI) with Advanced Network Analysis'' was to find brain mechanisms that underlie GWI. In pursuit of this goal, the tasks to be performed in Year 1 of this project were: 1) pre-processing of resting state fMRI (rsFMRI) data from 144 subjects; 2) performing group independent components analysis (ICA) on rsFMRI data of all suvbjects; and 3) labeling the resultant ICs of group ICA in terms of different brain functions they form constituent areas of. All these tasks were successfully accomplished in Year 1. Further, preliminary analysis of rsFMRI data from Control and Haley Syndrome 2 GWI subjects (in pursuant of aims of Year 2) revealed Syn2 exhibited clear deficits in brain communication in networks of the brain responsible for visual processing, mood regulation, motor coordination, sensory processing, and language command, but increased communication in networks related to pain perception during rest, consistent with self-reported symptoms.

**15. SUBJECT TERMS**
Gulf War Illness; Haley GWI Syndromes 1, 2, and 3; neurologic symptoms, neurocognitive; affective; pain; sensory; resting state functional MRI; independent components analysis

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## INTRODUCTION

An estimated 25% to 32% of 1991 Gulf War veterans experience multi-symptom conditions not explained by stress or psychiatric illness (1). Affecting up to 200,000 veterans deployed to Iraq, Kuwait, and Saudi Arabia during the 1991 Persian Gulf War, this poorly understood chronic medical condition referred to as Gulf War Illness (GWI), comprises a variety of behavioral and neurological symptoms and complaints including fatigue, generalized neuropathic pain, memory and concentration deficits, vestibular disturbances, and depression. The objective/goal of this project titled, "Exploring Brain Mechanisms Underlying Gulf War Illness with Advanced Network Analysis" was to find brain mechanisms that underlie GWI. This search for mechanisms of GWI was to be accomplished by mapping the whole-brain functional connectivity network architecture of GWI veterans, through group independent components analysis (ICA), and comparing them with age-matched veteran controls.

**KEYWORDS:** Gulf War Illness; Haley GWI Syndromes 1, 2, and 3; neurologic symptoms, neurocognitive; affective; pain; sensory, resting state functional MRI (rsFMRI); resting state functional connectivity; independent components analysis (ICA),

## ACCOMPLISHMENTS

***Major goals of the project in Year 1***

According to the approved **Statement of Work** for the aims and goals for Year 1 of the GWIRP project Exploring Brain Mechanisms Underlying Gulf War Illness through Advanced Network Analysis are (see also Table 1; which lists the Aims and Tasks by Quarter):

**Specific Aim1:** To comprehensively extract all resting state networks (RSNs), including those corresponding to each of the functional domains implicated by GWI symptoms and neurocognitive assessments through independent component analysis (ICA) of rsFMRI data from veterans with Haley GWI Syndromes 1, 2, and 3, and controls. Further, to obtain voxel-level and network-level measures of network strength.

Under which the Tasks to be performed were,

Aim1:Task1: Preprocessing of rsFMRI data. This includes physiological noise correction, image registration, spatial normalization to MNI template space, motion-artifact correction, low pass filtering, and spatial smoothing. This also includes quality assessment and control of data at all stages mentioned.

Aim1:Task2: Performing Group ICA to extract brain resting state networks.

Aim1:Task3: Template matching sorting of ICs to find ICs that constitute each of the networks implicated in GWI.

*Table 1: Schedule of work in the project by quarters (Q).*

| **Tasks (Persons)** | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 |
|---|---|---|---|---|---|---|---|---|
| Specific Aim1:Task1 | X | X | | | | | | |
| Specific Aim1:Task2 | | X | X | X | | | | |
| Specific Aim1:Task3 | | X | X | X | | | | |
| Specific Aim2:Task1 | | | | X | X | X | X | X |
| Specific Aim2:Task2 | | | | X | X | X | X | X |
| Specific Aim2:Task3 | | | | X | X | X | X | X |
| Dissemination of Results | | | | X | X | X | X | X |

***Accomplishments under the major goals of the project in Year 1***

We accomplished all the action items listed under the major goals. Below is a task-by-task description of accomplishments. The major activities, are the three tasks under Aim1 listed above and below. The specific objectives pertaining to each task is described under the said task.

Aim1:Task1: Preprocessing of rsFMRI data.

The data for this project consisted of well-controlled rsFMRI and supporting anatomy data from 144 subjects scanned under the Department of Veterans Affairs IDIQ contract VA549-P-0027 with University of Texas Southwestern Medical Center (UTSWMC), between 2008-2009. Of these 45 were controls, 30 with Syn1, 38 with Syn2 and 31 with Syn3.For each subject, the MRI dataset included

1) Whole-brain resting state fMRI dataset (eyes open condition); TR/TE/FA = 2000ms/24ms/80°; voxel size 3mm X 3mm; slice thickness = 3mm.

2) Whole-brain T1w 3D MPRAGE dataset; TR/TI/TE/FA = 2250ms/900ms/3ms/9°; 0.9 mm X 0.9mm X 1mm voxels.

We processed the rsfMRI and T1-weighted (T1w) anatomic data from all *143* subjects in the study. We employed AFNI (2) and FSL (3) software for pre-processing. Each subject's high-resolution T1w anatomic was aligned to the MNI152 template (4) with both an affine registration algorithm (5) implemented through FSL's *flirt* program, followed by a nonlinear free-formed deformation based warping through FSL's *fnirt* program. Figure 1 shows an example T1w anatomic scan (1a) for a GW subject, and rsFMRI scan (1b) aligned to MNI152 template.

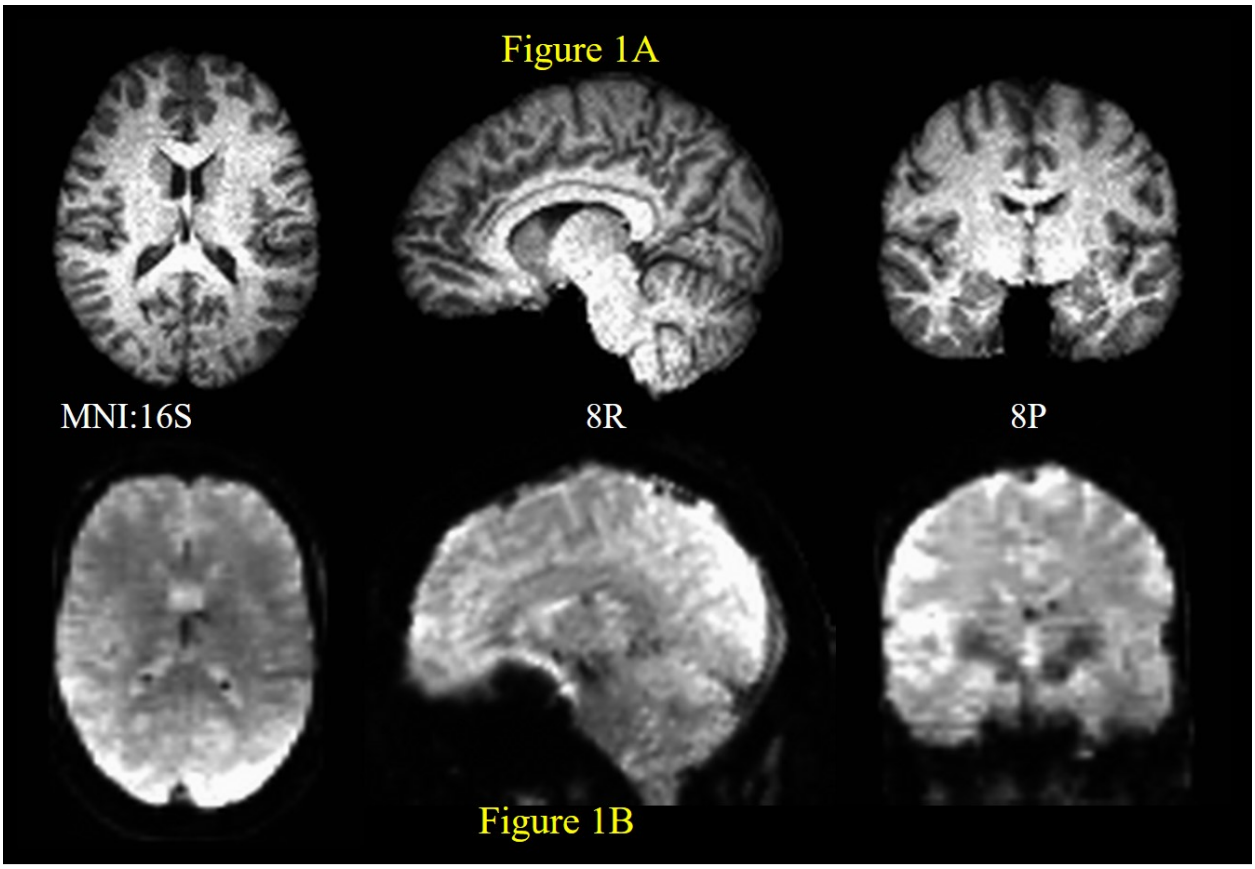


Figure 1: (A) T1w anatomic and (B) rsfMRI scans from a representative subject after alignment to MNI 152 space.

For each subject, the rsFMRI voxel time-series were temporally shifted to account for differences in slice acquisition times with and AFNI's 3dTshift program. Then the 3D volumes of the rsfMRI time-series were registered to a base volume to account for global rigid motion with an image intensity-based least squares algorithm (6) implemented in AFNI's *3dvolreg* program. The volume-registered time-series were corrected for motion, and physiological artifacts using the advanced ICA-AROMA technique (7, 8). The pre-processed and denoised time-series were then co-registered to the T1w anatomic scan using the well-established affine boundary based registration algorithm (9) implemented through FSL's *flirt* program, followed by alignment to the MNI152 template through the warp computed between the subject's T1w anatomic and the MNI152 template.

Aim1 Task2: Performing Group ICA to extract brain resting state networks:

The following group ICA based comparisons were performed.

1) GWI Syn1 v Controls
2) GWI Syn2 v Controls
3) GWI Syn3 v Controls
4) All GWI veterans vs Controls
5) GWI vs Controls (CDC definition)
6) GWI vs Controls (Kansas case definition)

A group spatial ICA was performed on temporally concatenated data of the whole group of subjects (including controls and, GWI subjects of a given syndrome (e.g. Syn2) or all syndromes considered together (depending on the analysis selected)) (10), using the GIFT software (11, 12). Minimum description length (MDL) criteria will be used for automatic estimation of the number of ICs will be used. ICASSO utility of the GIFT software with random initialization and bootstrapping was used to determine the stability/reliability of the ICA and the number of ICs, running the ICA multiple times (10-20 times) software (11, 12). Since the MDL-based estimation of the number of ICs, can underestimate the number of ICs when there is heterogeneity in the nature of resting state brain networks in the combined group (as is the case when GWI subjects and Controls are consolidated into one group), we also tried a more conservative approach to estimating the number of ICs, by finding the MDL-based automatically estimated number of ICs for each group in the left and right hand sides of the 6 above-mentioned comparisons separately, and added the two numbers to arrive at the number of ICs to specific for the GIFT ICA command.

Aim 1 Task3: Template matching sorting of ICs to find ICs that constitute each of the networks in Table 2

MDL criteria-based automatic estimation of the dimensionality of the group ICA often yielded ICs which spanned a number of different brain functions. Hence we also employed higher dimensional ICA models by selecting the total number of ICs to be equal to the sum of MDL-based estimate of dimensionalities of the data from each syndrome groups/controls. This yielded more focal ICs. Most of the group ICs, did not lend themselves to simple brain networks listed in existing templates (e.g., (12-14)). Hence we labeled the ICs based on the extensive knowledge of brain function of one of the co-investigators (Professor Bruce Crosson). As an example, Table 1 lists some of the ICs obtained from Group ICA performed for the Syn2 vs Controls comparison. The brain areas represented in each of the ICs is listed in left column, with the corresponding brain function networks implicated on the right.

After completing the tasks listed in the Statement of Work for Year 1, we conducted some of the tasks scheduled for Year 2, specifically commencing the examination of differences in brain networks between GWI (especially Haley Syn2) and Controls. In course of this, we conducted some preliminary examinations in differences in between IC-network connectives in between GWI Syn2 and Control groups using a small sample of 22 GWI Syn2 and 30 Controls. Individuals with GWI Syn2 showed clear *deficits* in brain connectivity in networks of the brain responsible for visual processing, mood regulation, motor coordination, sensory processing, and language command, but *increased* connectivity in networks related to pain perception during rest. These result will be highlighted in a Press Conference at the Society for Neuroscience meeting. Further, we also performed as graph-based advanced network analysis so as to examine

functional connectivity differences between GWI and controls through another advanced network analysis method.

*Table 2: Independent Components derived from high dimensional group ICA on GWI Syn2 and Controls*

| Independent Components from GICA | Brain Function Network Labels |
|---|---|
| Left hemisphere: inferior frontal cortex (IFC), dorsolateral prefrontal cortex(dlPFC), angular gyrus (AG), supramarginal gyrus (SMG), pre-supplementary motor area (pre-SMA) | Language and semantic coding areas |
| Medial prefrontal cortex (mPFC), frontal polar cortex, pre-colossal anterior cingulate cortex (ACC), posterior cingulate cortex (PCC) | Action-outcome monitoring in default mode network (DMN) areas |
| Anterior temporal lobe (ATL), amygdala, hippocampus (Hb), | Limbic system areas |
| Frontal and striatal areas, ACC, insula, cerebellum | Front-striatal executive/cognitive control networks (ECN), salience network (SN) areas |
| mPFC, PCC, lateral parietal cortex, anterior inferior temporal region | DMN areas |
| Primary motor (M1) and somatosensory cortices (S1), SMA, paracentral lobule (PCL) | Sensorimotor function areas |
| Precuneus, and superior medial parieto-occipital cortices | Associative function areas |
| Brodmann areas (BA) 17, 18 and 19 | Unimodal visual cortex areas |
| Caudate, putamen, and nucleus accumbens | Basal ganglia functions |
| SMA, preSMA and cingulate | Motor programming areas |
| Occipito-temporal cortex, primary, and secondary visual cortices (V1, V2), inferior parietal lobule, all of inferior temporal gyrus, pulvinar | dorsal and ventral visual stream areas |

***Significant results or key outcomes***: Nothing to Report.

***Other Achievements***: Nothing to Report

***Opportunities for training and professional development***: Not applicable to this grant

***Dissemination of Results***:

The results from the project were disseminated at scientific conferences by Dr. Gopinath and Dr. Sakoglu in the form of scientific conference posters (see *Products* section). This process is ongoing with full papers scheduled to be submitted in Year 2.

***Plans for the next reporting period***: In the next reporting period we plan to perform the tasks and aims pertaining to Specific Aim 2 of our project (see also Table 1):

Specific Aim2: For each RSN listed in SA1, compare the integrity of the network between GWI veterans and age matched veteran controls in terms of network-level, and voxel-level measures of network strength: the goal being to comprehensively map the impairment of the network in each of the 3 GWI syndrome groups.

*SA2*: Sub-Aim1: To probe whether impaired network integrity in attention, executive function, working memory and episodic memory networks among GWI veterans is related to abnormally enhanced network strengths in chronic pain and affective networks among the same veterans.

*SA2*: Sub-Aim2: To examine the relationship between network integrity measures of RSNs corresponding to the networks listed in Table 2 and neurocognitive, psychiatric and autonomic testing assessments as applicable of the respective domains, to reveal the extent to which impairments in network integrity in GWI leads to deficits in behavioral assessments.

## IMPACT

Impact on the development of the principal discipline(s) of the project

There was no significant impact on the principal disciplines of the project, based on the tasks scheduled for Year 1, since they only included pre-processing and group ICA in support of the different statistical tests scheduled to be performed in Year 2 to extract brain mechanisms of GWI.

***Impact on other disciplines***: Nothing to report

***Impact on technology transfer***: Nothing to report

***Impact on society beyond science and technology***: Nothing to report

## CHANGES/PROBLEMS

***Changes in approach and reasons for change***:

There were no significant problems encountered. Thus, there were no significant changes to the approach. We performed group ICA with a large number of ICs than yielded by MDL criteria in order to increase the intra-cluster similarity, yielding more functionally specific group ICs. Further, since the some of the group ICs (see Figures, Tables) generated from ICs, did not lend themselves to simple brain networks listed in existing templates (e.g., (12-14)). Hence we labeled them based on the extensive knowledge of brain function of one of the co-investigators (Professor Bruce Crosson). This change has led to some generation of some exciting results in the examination of differences in between IC-network connectives in between GWI Syn2 and Control subjects (see *Accomplishments* section).

## PRODUCTS

**Other publications, conference papers, and presentations**

We presented two conference posters based on our project. We also published the conference abstracts corresponding to these posters.


1) Gopinath K, Thapa-Chetry B, Ouyang L, Krishnamurthy L, Krishnamurthy V, Goyal A, Gandhi P, Fang Y, Sakoglu U, Crosson B, Haley R. Gulf War Illness patients exhibit impaired/abnormal connectivity in multiple brain rsFMRI networks. Proc Org Hum Brain Mapp. 2017;22:3069
2) Gopinath K, Thapa-Chetry B, Ouyang L, Krishnamurthy L, Krishnamurthy V, Goyal A, Gandhi P, Fang Y, Sakoglu U, Haley R. Gulf War Illness Patients Exhibit Impaired Connectivity in Multiple Brain Function Networks Consistent with Chronic Multi-Symptom Illness: A Resting State fMRI Study. Proc Intl Soc Mag Reson Med. 2017;25:4191.

## PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### Emory University Personnel

| **Name** | **Kaundinya Gopinath, PhD.** |
|---|---|
| Project Role | Principal Investigator (PI) of the DoD award |
| Research Identifier | ERA Commons: KGOPIN |
| Nearest person month worked: | 4.8 calendar months |
| Contribution to Project: | Dr. Gopinath took part in all three tasks in Year 1. He shared data analysis duties with Dr. Sakoglu (of UHCL, see *Other Collaborating Organizations*). He also designed data analysis methodology adopted in the project in collaboration with Dr. Sakoglu. He also hosted Dr. Sakoglu's scientific collaboration visit to Emory University as budgeted, and made a visit to Dr. Haley's (of UTSWMC see *Other Collaborating Organizations*) lab in UTSWMC (see *Other Collaborating Organizations*) to obtain Dr. Haley's insights on the results, as well as obtain behavioral and clinical testing data for Year 2, and get insights on the different tests performed on the GW cohort. Further he attended Organization of Human Brain Mapping, 2017 conference to disseminate results from the project. |
| Funding Support | NA (funded by DoD award for this project) |

| **Name** | **Bruce Crosson, PhD.** |
|---|---|
| Project Role | Co-Investigator |
| Research Identifier | ERA Commons: BCROSSON |
| Nearest person month worked: | 1.2 calendar months |
| Contribution to Project: | Dr. Crosson took charge of making sure that the ICs yielded by group ICA analysis in Aim1 were labeled correctly in terms of what brain function networks were being represented by each IC. He also provided critical insights into the results of the project and suggested interesting analyses we could pursue in Year 2. |
| Funding Support | NA (funded by DoD award for this project) |

**Other collaborating Organization 1:**

**Organization 1 Name**: University of Houston Clear-Lake (UHCL)

**Location of Organization 1:** Address: Delta Annex (DA) Building, Room 8, 2700 Bay Area Blvd, Houston, TX 77058

**Partner's contribution to the project**: Collaboration through Emory-UHCL sub-contract under the DoD award for this project.

**UHCL Sub-Contract Personnel**

| **Name** | **Unal Sakoglu, PhD.** |
|---|---|
| Project Role | PI of UHCL sub-contract |
| Research Identifier | ERA Commons: KGOPIN |
| Nearest person month worked: | 3.49 calendar months |
| Contribution to Project: | Dr. Sakoglu help Dr. Gopinath design the data analysis methodology adopted in the project. He also shared data analysis responsibilities with Dr. Gopinath on all three tasks, with more emphasis on Task 2 and Task 3, relating to group ICA. Dr. Sakoglu created Matlab scripts to run the group ICA analysis. He also visited to Emory University for scientific collaboration as budgeted, and made a visit to Dr. Haley's (of UTSWMC see *Other Collaborating Organizations*) lab in UTSWMC (see *Other Collaborating Organizations*) along with Dr. Gopinath for scientific collaborations budgeted on this project. Further he attended International Society for Magnetic Resonance in Medicine, 2017 conference to disseminate results from the project. |
| Funding Support | NA (funded by DoD award Emory-UHCL sub-contract for this project) |

**Other collaborating Organization 2:**

**Organization 2 Name**: University of Texas Southwestern Medical Center (UTSWMC)

**Location of Organization 2:** Address: 5323 Harry Hines Blvd., Dallas, TX 75390

**Partner's contribution to the project**: Collaboration through Emory-UTSW sub-contract under the DoD award for this project.

**UTSWMC Sub-Contract Personnel**

| **Name** | **Robert Haley, MD.** |
|---|---|
| Project Role | PI of UTSWMC sub-contract |
| Research Identifier | ERA Commons: RHALEY |
| Nearest person month worked: | 1.8 calendar months |
| Contribution to Project: | Dr. Haley provided the de-identified MRI data required for this project. Further he provided valuable insights into results of the project and provided ideas for further analyses in Year 2. He also provided some of the behavioral testing and clinical data needed for the Aims of Year 2. He also hosted Dr. Gopinath and Dr. Sakoglu on their scientific collaboration visit to UTSWMC budgeted in the project. |
| Funding Support | NA (funded by DoD award Emory-UTSW sub-contract for this project) |

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